

Diabetes and Back Pain: Markers of Diabetes Disease Progression Are Associated With Chronic Back Pain

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IN BRIEF Diabetes has been associated with the incidence of back pain. However, the relationship between markers of diabetes progression and back pain has not been studied. The objective of this study was to correlate clinical and laboratory measures of diabetes disease severity to the presence of back pain to provide insight into the relationship between these conditions. Findings showed that markers of diabetes disease progression were associated with the presence of back pain, suggesting that uncontrolled diabetes may contribute to the development of chronic back pain.

Introduction

Uncontrolled type 1 or type 2 diabetes negatively affects multiple organ systems, with well-known cardiovascular, renal, ophthalmological, and neurological sequelae of disease (1). Although it is generally accepted that these manifestations are rooted in micro- and macrovascular pathophysiological changes, the full extent of the effects of prolonged hyperglycemia is not yet completely understood.

Recent studies have suggested that chronic back pain (CBP) is more prevalent in patients with diabetes (2). Numerous studies have found a link between hyperglycemia and the biochemical events that may underlie intervertebral disc degeneration (3–11), thus providing a potential mechanism by which diabetes may contribute to CBP. In addition, these results suggest that the likelihood of CBP may increase with disease severity, which can be estimated by the degree to which a patient's diabetes is uncontrolled.

Laboratory surveillance for the development of diabetes-related complications includes biannual (or more frequent) A1C measurement, as well as periodic measurement of serum lipid levels and renal function tests. Patients

are also monitored for the development of obesity, retinopathy, and neuropathy (12). These data points provide a cumulative measurement of a patient's overall diabetes-related disease burden. Herein, we performed a retrospective cohort analysis of patients with diabetes segregated into three groups: those with diabetes but without CBP, those with both diabetes and CBP, and those with diabetes, CBP, and a history of spinal surgery. The objective of the study was to determine whether markers of increased diabetes disease burden were associated with clustering into one of these three cohorts.

Methods

Patient Identification

Patients diagnosed with either type 1 or type 2 diabetes between the years of 1997 and 2010 were identified within our institution's clinical database using the International Classification of Diseases (ICD)-9 codes 249, 250, E10, and E11. Within this group, patients also suffering from CBP were identified using the ICD.9 code 724.2. It was then determined whether patients with both diabetes and back pain underwent a surgical spine procedure using ICD-9 procedural codes 03.0,

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TABLE 1. Patient Demographic and Operative Characteristics

	Patients for Whom Data Were Available (n)	Percentage of Patients for Whom Data Were Available (%)	Value
Mean age at diabetes diagnosis (years [SD])	67,132	100.00	63.2 (14.8)
Mean diabetes duration (days [SD])	67,132	100.00	2,602.8 (1137.0)
Mean BMI (kg/m ² [SD])	59,688	88.9	34.5 (9.0)
Sex (n [%])	67,132	100.00	
Male			37,907 (56.5)
Female			29,225 (43.5)
Back status category (n [%])	67,132	100.00	
No CBP			57,064 (85.0)
CBP, no surgery			9,137 (13.6)
CBP, surgery			931 (1.4)
Diabetes type (n [%])	67,132	100.00	
Type 1			4,924 (7.3)
Type 2			62,208 (92.7)
Medication use (n [%])	67,132	100.00	
Insulin			30,912 (46.0)
Metformin			26,993 (40.2)
Comorbidities (n [%])	67,132	100.00	
Neuropathy			9,772 (14.6)
Retinopathy			7,295 (10.9)
Hypertension			43,975 (65.5)
Mean laboratory values*			
A1C (% [SD])	51,219	76.3	7.5 (1.9)
LDL cholesterol (mg/dL [SD])	49,393	73.6	131.13 (96.3)
HDL cholesterol (mg/dL [SD])	50,905	75.8	40.47 (14.2)
Triglycerides (mg/dL [SD])	51,639	76.9	267.07 (365.3)
Total cholesterol (mg/dL [SD])	51,725	77.1	218.66 (69.9)
Serum creatinine (mg/dL [SD])	63,313	94.3	1.79 (1.8)
Urine albumin/creatinine (mg/g [SD])	25,346	37.8	315.52 (1,483.8)

*Mean of highest (or lowest, in the case of HDL) recorded value.

03.09, 80.51, 81.0, 81.01–81.05, 81.07, 81.3, 81.62, 84.51, 84.6, and 84.61–84.69. Patients' demographic information, BMI, comorbid conditions, diabetes-related complications, medication use, and laboratory test results were then collected.

Laboratory Values and BMI

Laboratory tests of interest included A1C, LDL cholesterol, HDL cholesterol, triglycerides, total cholesterol, serum creatinine, and urine albumin/creatinine ratio. To obtain a measure

of disease control, as well as a measure of the degree to which known diabetes complications had progressed, we documented the "worst" value recorded for each test after the initial diagnosis of diabetes. For most tests, this was represented by the highest value; for HDL, it was the lowest value. The highest recorded BMI was also documented for each patient.

Statistical Analysis

Statistical analysis was performed using Stata Statistical Software, Release

14 (StataCorp, College Station, Tex.). Analysis of variance and χ^2 tests were performed for unadjusted analysis of continuous and categorical variables, respectively. Multinomial logistic regression analysis using a backward stepwise selection algorithm was used for multivariable analysis to determine whether patients' laboratory, clinical, and demographic variables were associated with segregation into one of the three cohorts of interest. The alpha level for statistical significance was set at 0.05.

TABLE 2. Surgical Procedures

	Mean Age (years [SD])	Sex		Diabetes		Mean Diabetes Duration (days [SD])
		Male (%)	Female (%)	Type 1 (%)	Type 2 (%)	
All procedures	65.5 (14.0)	60.4	39.6	4.3	95.7	643.8 (2,724.4)
Decompressive laminectomy	70.3 (13.9)	66.1	33.9	3.1	96.9	927.7 (3,854.6)
Lumbar discectomy	60.5 (14.3)	57.5	42.5	5.6	94.4	407.6 (1,504.5)
Posterior thoracolumbar fusion	65.3 (10.7)	49.0	51.0	3.9	96.1	553.8 (1,359.3)
Anterior thoracolumbar fusion	60.2 (11.1)	68.0	32.0	4.0	96.0	335.2 (898.2)
Posterior cervical fusion	66.5 (11.1)	66.7	33.3	5.6	94.4	436.2 (1,397.6)
Anterior cervical fusion	58.2 (11.3)	57.7	42.3	7.7	92.3	287.0 (1,519.9)
Atlanto-axial fusion	54.0 (7.8)	66.7	33.3	0.0	100.0	471 (1,701.2)

Results

A total of 67,132 patients within our institutional database were identified as having the diagnosis of either type 1 or type 2 diabetes. These patients had a mean age of 63.2 years at initial diabetes diagnosis, and 43.5% of them were female. A large majority of patients (92.7%) had type 2 diabetes. The average duration of diabetes, calculated using the date of first diagnosis and date of either last follow-up or death, was 2,602.8 days (7.1 years). The mean highest recorded BMI was 34.5 kg/m². Of all patients with diabetes, 13.6% (9,137) had a diagnosis of CBP but did not have spinal surgery; 1.4% of patients (931) carried a diagnosis of CBP and received spinal surgery. Additional information on patient demographics, comorbid conditions, prevalence of diabetes-related complications, and laboratory test results is presented in Table 1. Information on the type of surgery received by patients in the surgical cohort can be found in Table 2.

On unadjusted analysis, patients with diabetes, CBP, and a history of spinal surgery were significantly associated with a number of observed variables (Table 3). The mean duration of time since original diabetes diagnosis increased in a stepwise manner from patients with diabetes who did not have CBP (2,554.6 days [7.0 years]) to those with diabetes who had CBP but no history of spinal surgery (2,857.0 days [7.8 years]) to those

with diabetes who had both CBP and a history of spinal surgery (3,065.7 days [8.4 years]; *P* < 0.001). The incidence of hypertension was greater among patients with CBP (80.0%) and those with CBP who underwent spinal surgery (88.6%) than among those without CBP or spinal surgery (62.8%; *P* < 0.001). Similarly, the incidence of neuropathy was greater among patients with CBP (20.1%) and those with CBP who underwent spinal surgery (32.0%) than among those without CBP (13.4%; *P* < 0.001). Finally, the incidence of retinopathy was greater among patients with CBP (14.7%) and patients with CBP who underwent spinal surgery (14.8%) than among patients without CBP (10.2%; *P* < 0.001).

The highest recorded BMI was greater in patients with CBP (36.7 kg/m²) and those with CBP who underwent spinal surgery (36.6 kg/m²) than in those without CBP (34.1 kg/m²; *P* < 0.001). The highest recorded A1C was significantly greater in patients with CBP (7.8%) and those with CBP who underwent spinal surgery (7.8%) than in those without CBP (7.4%; *P* < 0.001). The highest recorded LDL cholesterol value was greater in patients with CBP (168.7 mg/dL) and those with CBP who underwent spinal surgery (166.6 mg/dL) than in those without CBP (122.8 mg/dL; *P* < 0.001). The same trend was apparent for mean total

cholesterol levels, with higher values observed in patients with CBP (235.9 mg/dL) and those with CBP who underwent spinal surgery (237.7 mg/dL) than in those without CBP (214.9 mg/dL; *P* < 0.001). Triglyceride levels were also significantly greater in patients with CBP (314.0 mg/dL) and those with CBP who underwent spinal surgery (364.3 mg/dL) than in those without CBP (256.0 mg/dL; *P* < 0.001). Conversely, the mean lowest recorded HDL cholesterol value was significantly lower in patients with CBP (38.5 mg/dL) and those with CBP who underwent spinal surgery (36.7 mg/dL) than in those without CBP (40.9 mg/dL; *P* < 0.001). Insulin usage was more common in patients with CBP who underwent spinal surgery (50.7%) than in those without CBP (46.0%, *P* < 0.001). Metformin usage was also more common in patients with CBP (49.9%) and those with CBP who underwent spinal surgery (56.2%) than in those without CBP (38.4%; *P* < 0.001).

Associations between metrics of diabetes disease burden and the presence of CBP with and without spinal surgery were evaluated in a risk-adjusted manner using multinomial logistic regression analysis (Table 4). Each additional year of age at the time of diabetes diagnosis was associated with an increase in the log odds of CBP relative to patients with diabetes but without CBP (log odds 0.01, 95% CI 0.007–0.013).

TABLE 3. Bivariate Analysis

	Diabetes, No CBP	Diabetes and CBP	Diabetes, CBP, and Spinal Surgery	P
Total patients with diabetes by category (n [%])	57,064 (100.0)	9,137 (100.0)	931 (100.0)	
Type 1 diabetes (n [%])	4,461 (7.8)	423 (4.6)	40 (4.3)	<0.001
Type 2 diabetes (n [%])	52,603 (92.2)	8,714 (95.5)	891 (95.7)	<0.001
Female sex (n [%])	24,359 (42.7)	4,497 (49.2)	369 (39.6)	<0.001
Neuropathy (n [%])	7,637 (13.4)	1,837 (20.1)	298 (32.0)	<0.001
Retinopathy (n [%])	5,811 (10.2)	1,346 (14.7)	138 (14.8)	<0.001
Hypertension (n [%])	35,840 (62.8)	7,310 (80.0)	825 (88.6)	<0.001
Insulin use (n [%])	26,255 (46.0)	4,185 (45.8)	472 (50.7)	<0.001
Metformin use (n [%])	21,912 (38.4)	4,558 (49.9)	523 (56.2)	<0.001
Age at diabetes diagnosis (years)	63.1	63.5	63.7	0.0326
Diabetes duration (days)	2,554.6	2,857.0	3,065.7	<0.001
BMI (kg/m ²)	34.1	36.7	36.6	<0.001
A1C (%)*	7.4	7.8	7.8	<0.001
LDL cholesterol (mg/dL)*	122.8	168.7	166.6	<0.001
HDL cholesterol (mg/dL)*	40.9	38.5	36.7	<0.001
Triglycerides (mg/dL)*	256.0	314.0	364.3	<0.001
Total cholesterol (mg/dL)*	214.9	235.9	237.7	<0.001
Serum creatinine (mg/dL)*	1.8	1.9	1.8	<0.001
Urine albumin/creatinine (mg/g)*	306.5	352.4	255.2	0.080

*Mean of highest (or lowest, in the case of HDL) recorded value. Boldface P values indicate statistical significance.

Similarly, increased time between initial diabetes diagnosis and date of last follow-up was independently associated with an increase in the log odds of CBP (log odds 0.0002, 95% CI 0.0001–0.0002) and CBP requiring spinal surgery (log odds 0.0004, 95% CI 0.0003–0.0005) relative to patients with diabetes who had neither CBP nor spinal surgery. Medical comorbidities independently associated with an increased log odds of CBP included hypertension (log odds 0.359, 95% CI 0.264–0.454) and diabetic neuropathy (log odds 0.282, 95% CI 0.194–0.369). However, having a diagnosis of diabetic retinopathy was associated with a reduction in the log odds of surgical intervention (log odds –0.471, 95% CI –0.716 to –0.225) relative to patients with diabetes but without CBP or surgery. Each point increase in BMI was independently associated with CBP (log odds 0.018, 95% CI 0.015–0.022) and CBP with

spinal surgery (log odds 0.01, 95% CI 0.001–0.02) relative to patients with diabetes without CBP or surgery. Increases in each additional point of maximum A1C (log odds 0.055, 95% CI 0.037–0.073), LDL cholesterol (log odds 0.004, 95% CI 0.003–0.004), and triglycerides (log odds 0.0001, 95% CI 0.00005–0.0002) were independently associated with CBP. Each point increase in the lowest recorded HDL cholesterol value was independently associated with a decrease in the log odds of CBP (log odds –0.007, 95% CI –0.01 to –0.0002). Each point increase in the maximum recorded LDL level (log odds 0.004, 95% CI 0.003–0.005) and triglycerides (log odds 0.0003, 95% CI 0.0001–0.0004) was independently associated with an increase in the log odds of CBP and spinal surgery. Increased levels of HDL cholesterol were independently associated with decreased log odds of CBP and spinal surgery (log odds –0.013

(95% CI –0.022 to –0.004). Finally, metformin use was independently associated with increased log odds of CBP (log odds 0.116, 95% CI 0.046–0.187) and CBP that required spinal surgery (log odds 0.378, 95% CI 0.175–0.580).

Discussion

In the past decade, the incidences of both type 1 and type 2 diabetes have been rising among children and adolescents (13,14), suggesting that, over time, an increasing segment of the population will suffer the complications of this chronic disease. This study demonstrated that metrics of diabetes disease burden were increased in patients with diabetes and CBP and in patients with diabetes, CBP, and a history of spinal surgery relative to patients with diabetes but without CBP. These results suggest that chronic, uncontrolled diabetes may be a contributing factor to the

TABLE 4. Results of Multivariable Logistic Regression Analysis

	Log Odds	95% CI	P
<i>Patients with diabetes and CBP but with no history of spinal surgery</i>			
Type 2 diabetes	0.251	0.091–0.411	0.002
Female sex	0.332	0.265–0.399	<0.001
Neuropathy	0.282	0.194–0.369	<0.001
Retinopathy	–0.016	–0.110 to 0.078	0.737
Hypertension	0.359	0.264–0.454	<0.001
Insulin use	–0.2	–0.274 to –0.127	<0.001
Metformin use	0.116	0.046–0.187	0.001
Age at diabetes diagnosis	0.01	0.007–0.013	<0.001
Diabetes duration	0.0002	0.0001–0.0002	<0.001
BMI	0.018	0.015–0.022	<0.001
A1C	0.055	0.037–0.073	<0.001
LDL cholesterol	0.004	0.003–0.004	<0.001
HDL cholesterol	–0.007	–0.01	<0.001
Triglycerides	0.0001	0.00005–0.0002	0.002
<i>Patients with diabetes and CBP and a history of spinal surgery</i>			
Type 2 diabetes	0.24	–0.212 to 0.693	0.289
Female sex	–0.018	–0.206 to 0.170	0.848
Neuropathy	0.995	0.787–1.204	<0.001
Retinopathy	–0.471	–0.716 to –0.225	<0.001
Hypertension	0.852	0.514–1.189	<0.001
Insulin use	0.057	–0.146 to 0.260	0.582
Metformin use	0.378	0.175–0.580	<0.001
Age at diabetes diagnosis	0.007	–0.0004 to 0.015	0.063
Duration of diabetes	0.0004	0.0003–0.0005	<0.001
BMI	0.01	0.001–0.020	0.036
A1C	–0.028	–0.810 to 0.024	0.292
LDL cholesterol	0.004	0.003–0.005	<0.001
HDL cholesterol	–0.013	–0.022 to –0.004	0.004
Triglycerides	0.0003	0.0001–0.0004	0.001

Boldface P values indicate statistical significance.

development of CBP and potentially of CBP that ultimately necessitates surgical intervention.

Our results suggest that higher A1C levels are associated with the presence of CBP. Recent animal studies have investigated the relationship between hyperglycemia and intervertebral disc degeneration. In a rat model, hyperglycemia was found to promote disc autophagy and to accelerate the rate of stress-induced senescence in nucleus pulposus cells, both of which may contribute to disc

prolapse and the onset of mechanical back pain (15). Another mechanism may be the microvascular disease that is the hallmark of diabetes. The intervertebral disc is an avascular structure, depending on simple diffusion from the cartilaginous endplates of the vertebral bodies for nutrition. Studies have found decreased microvessel diameter within the endplates of diabetic rats. In addition, decreased microvessel diameter was associated with disc degeneration (7). Further work will be needed to fully

understand the mechanism by which diabetes contributes to CBP.

Interestingly, type 2 diabetes was found to be an independent predictor of CBP relative to type 1 diabetes. Insulin resistance and subsequent hyperinsulinemia are characteristic of type 2 diabetes (1). Hyperinsulinemia has been associated with increased levels of the proteoglycan chondroitin sulfate within intervertebral discs in weaning rats (3). Change in the relative composition of proteoglycans within the disc matrix has been associated with disc degeneration, offering at least a partial explanation of how type 2 diabetes may predispose patients to CBP (4,5). However, we also found that the use of exogenous insulin was negatively associated with CBP. This may be partially explained by the fact that all patients with type 1 diabetes require insulin therapy. In addition, although insulin is often a second- or even third-line therapy for type 2 diabetes, its use may finally lead to adequate glycemic control in these patients. Overall, type 2 diabetes is a complex disease and is likely to contribute to CBP through multiple mechanisms. Moreover, the use of insulin may both positively and negatively correlate with CBP, depending on the clinical context.

We also found associations between cholesterol levels and CBP. Of note, whereas elevated LDL cholesterol was associated with CBP, elevated HDL was negatively associated with this outcome, suggesting that a favorable cholesterol profile may reduce the risk of CBP in patients with diabetes. These associations were present even after controlling for age, A1C level, and BMI. A link between serum lipid levels and back pain is controversial (16), although several epidemiological studies have found increased HDL cholesterol to be negatively associated with CBP (17,18). It is possible that advanced atherosclerosis also contributes to the microvessel disease that leads to disc degeneration (7). More work is needed to determine whether

and how cholesterol levels participate in the pathophysiology of CBP.

A small subset of patients within our larger cohort included patients with diabetes and CBP who had a history of spinal surgery. The average laboratory values of these patients, particularly A1C, were similar to those of patients with diabetes and CBP who did not have spinal surgery. Of note, diabetes duration was also associated with spinal surgery, again suggesting that the cumulative effect of diabetes over time may contribute to the degenerative changes that cause pain and at times necessitate surgical intervention. Interestingly, diabetes has been linked to the development of lumbar spinal stenosis (19,20). Future studies will be needed to determine how diabetes contributes to different spinal pathologies and whether there may be a causal relationship between increased diabetes disease burden and the need for spinal surgery.

Limitations

The average age at diagnosis of diabetes observed in the present study was significantly higher than the stated national average (1) (63.2 vs. 53.8 years). In addition, because of the cross-sectional nature of our study, it was not possible to accurately determine the relationship between laboratory test values and the onset of back pain. Moreover, we were unable to determine whether back pain was more likely to improve after normalization of abnormal laboratory test values. Although these are significant limitations, the aim of this study was to assess for a broad association between diabetes disease burden and CBP. In the future, smaller, more focused studies will be needed to address these more specific questions.

As with any study reporting data from a single institution, there is the possibility that these results are subject to surgeon selection bias. Because of the different surgical selection criteria and treatment algorithms used nationwide, patients with more advanced or complicated diabetes

may not be more likely to undergo surgical intervention at other institutions. Generally, however, severe diabetes disease burden and obesity with a BMI >40 kg/m² are considered relative contraindications to spinal surgery at our institution. Therefore, although our results show that diabetes seems to be more advanced in patients undergoing surgery, this should not be a reflection of disease progression to the point where a patient would be unable to try non-surgical interventions for CBP relief. In the future, a multi-institutional study may be helpful in determining the overall generalizability of our results to the population as a whole.

Conclusion

To our knowledge, we are the first to report an association between measures of diabetes disease burden and the presence of CBP. These results provide insight into the natural history of diabetes and highlight the need for a more in-depth investigation into how the degree of diabetes control relates to the onset, magnitude, and improvement of CBP.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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